AstraZeneca

Date: APR 11 2002

Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket Number 02D-0003
Response to FDA Call for Comments
Exercise-Induced Bronchospasm (EIB), Development of Drugs to Prevent EIB

Dear Sir or Madam:

Reference is made to the February 20, 2002, Federal Register notice announcing the availability of a draft guidance for industry entitled "Exercise-Induced Bronchospasm (EIB), Drug Development to Prevent EIB."

AstraZeneca has reviewed this guidance and our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to Richard Jahn, Regulatory Project Manager at (302) 885-8677.

Sincerely,

Richard Jahn for

Christopher M. Blango
Director
Regulatory Affairs
(302) 885-1809

CB\sg

Enclosure

02D-0003

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Comments from AstraZeneca on the FDA Draft Guidance for Industry Exercise-Induced Bronchospasm (EIB) – Development of Drugs to Prevent EIB

Comments are summarized below:

Section	Line Number	Comment or proposed replacement text
III. A.	73-74	The proposed guidance notes that EIB data should be generated with a dose ranging trial incorporating doses for the pediatric population. Please clarify why a dose ranging study is necessary if the dose has been previously established in the pediatric population. Please note that dose ranging work is not required to be repeated in the adult population.
III. A.	61-74	Please clarify if a single placebo-controlled trial is to be conducted within the dose-ranging trial or is it to be separate trial.
III. B.	78-86	The duration of the washout period can be as short as a "few days." Please quantify "few days."
III. B.	86	We suggest revising, "Ordinarily, any comparative claims should be replicated", to read, "A study needs to be replicated in order to support a comparative claim."
IV. A.	146-148	The category "nonsmokers" needs to be more restrictively defined. The guidance includes individuals not currently smoking and with a maximum 10-pack per year history. An individual with a prior smoking history would be at higher risk for pulmonary pathology than a non-smoker, bringing bias into the category. "Not currently smoking" needs further definition. Is this to include individuals who last smoked within 30 days of enrollment? Two weeks? In addition, does prior smoking history also include pipe and cigar smoking?
IV.A.	150-151	Consider clarifying following sentence, "Asthmatics should be stable, requiring only the occasional use of inhaled beta agonists for symptoms", so that it does not imply that prn short-acting beta agonist therapy is the only asthma therapy that eligible patients may be on.
IV.A.	157-158	We suggest revising "should demonstrate a decrease in FEV_1 with exercise of at least 20% from their baseline absolute FEV_1 value" to read, " . . . at least 20% from their baseline absolute FEV_1 value within one hour after exercise."
IV. A.	157-158	We recommend including the eligibility of patients who demonstrate a 20% fall from their baseline value on more than one occasion prior to randomization.
IV. A.	158-160	Recommend either deleting "Patients who require rescue medication following exercise or whose FEV_1s fall precipitously should be excluded from randomization", or revising to "Patients with a history of serious attacks of asthma precipitated by exercise should be excluded from randomization."
IV.D.	197-198	It is very important to add that baseline is measured before treatment is administered, as well, to the sentence, "Baseline FEV_1 is defined as the FEV_1 obtained just before each exercise challenge test." If treatment is administered 15 minutes before the challenge it is the pre-treatment value that is the baseline rather

		than any other value measured pre-exercise (but potentially post-treatment) This issue is particularly important to consider when testing a drug with rapid and dramatic bronchodilating effects. The important and well-documented statistical issues associated with choosing a baseline value measured after treatment has been administered should be addressed in detail in this guidance. The current guidance might well lead to misleading and/or uninterpretable analyses. See Senn, S J. 'The use of baselines in clinical trials of bronchodilators', Statistics in Medicine, 8, 1339-1350 (1989). In addition, the guidance should provide justification for recommending an analysis based on a % change from baseline rather than on absolute FEV_1 values (in liters).
IV.D.	189-216	This section mentions "two analyses" (lines 189-190) and that an "important secondary analysis of FEV_1 is to categorize for each treatment the percentage of patients whose FEV_1 falls by a specified amount from baseline" (lines 204-205). Specifically, the last sentence (lines 212-216) states the following: "If a drug (versus placebo) shows a statistically significant effect for the primary analysis of mean maximal percentage fall in FEV_1 for the group, but the drug fails to show a meaningful improvement in patient responses for the categorical analysis, the results would be a review issue of concern." In order for sponsor companies to optimize the utilization of the guidance, it will be critical for the FDA to clearly state their expectation related to statistical issues. 1. Do these endpoint/analyses need to be pre specified as co-primary? Please clarify the inconsistency found on line 190, which implies co-primary endpoints should be specified, whereas line 213 refers to a "primary analysis of mean maximal percentage fall....". 2. Does a formal inferential statistical analysis of the categorization of drop in FEV_1 need to be performed, or is it a descriptive presentation? 3. What constitutes a "meaningful improvement" in the analysis of the categorization of drop in FEV_1? 4. Address sample size considerations resulting from this guidance. For a given power, the analysis of the categorical variables will likely require more patients. 5. Address multiplicity (ie, overall Type I error control) issues resulting from this guidance. It seems reasonable that a stepwise approach would be acceptable if inferential testing is required for both analyses. That is, if statistical significance (at 0.05) is achieved for the primary variable, then the secondary variable could also be tested at the nominal 0.05 level.
IV.D.	206-216	AZ recommends to include other secondary endpoints such as time to recovery and "AUC" over 60 minutes which are not mentioned in the guidance but have been used standardly in other studies. These analyses would be able to employ the same mean data as the primary endpoint.
IV. E.	226-230	The guidance states, "if patients do not return to an FEV_1 that is at least within 20% of their baseline, they should not continue in the exercise protocol." Clarify timing for which the patient must return to that 20% of their baseline and whether rescue beta-agonist might be utilized to facilitate the return to within 20% of baseline.

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